

Classical diseases revisited: transient global amnesia

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Transient global amnesia usually affects patients between the ages of 40 and 80. Patients with this condition are often described – wrongly – as being confused. It presents classically with an abrupt onset of severe anterograde amnesia. It is usually accompanied by repetitive questioning. The patient does not have any focal neurological symptoms. Patients remain alert, attentive, and cognition is not impaired. However, they are disoriented to time and place. Attacks usually last for 1–8 h but should be less than 24 h. It is possible that it may result from different mechanisms such as venous congestion with valsalva-like activities before symptom onset, arterial thromboembolic ischaemia and vasoconstriction due to hyperventilation. Diagnosis may be made safely in the presence of a characteristic collateral history. No specific treatment is indicated for a typical episode.

During the episode, all patients are unable to lay down new memories (verbal and non-verbal), and thus experience profound anterograde amnesia. Retrograde amnesia is often present but is of variable duration, which can range from a few hours up to years. The episodes occur in clear consciousness, patients remain fully communicative and alert throughout, and often carry out complex tasks like driving and playing music. However, they are often agitated or anxious, and may repeat the same questions (mostly relating to orientation) every few minutes. Occasionally, TGA is accompanied by headache, dizziness, nausea and vomiting. Immediate recall is unaffected as is memory relating to personal details. Higher cortical functions such as language, calculations, visuospatial skills, reasoning and abstract thinking are intact. There are no focal neurological signs.

At the cessation of the attack, there is a rapid and apparently complete return of anterograde memory. On formal testing, minor changes in anterograde memory may persist for months, although this is unlikely to be detected clinically. In contrast, retrograde memory is slower to return to normal, with most recent memories returning last. As patients cannot lay down new memories during the attack, they will never be able to recall the episode itself.

Transient global amnesia (TGA) is an intriguing clinical entity. For the patients and relatives it is a very traumatic event. Many clinicians would not have encountered it, and those not familiar with its presentation can miss the diagnosis. In this article, we give an overview of this classical condition, focusing on the differential diagnosis and recent developments.

TGA is a clinical syndrome first described in 1956 and characterised by an inability to form new memories described as anterograde amnesia. It is often associated with retrograde amnesia and has an incidence of 5 per 100 000 population per year. It usually affects patients between the ages of 40 and 80 years, at an average age of 61 years.¹ It has no male or female preponderance.

CLINICAL PRESENTATION

Many case reports were published before diagnostic criteria were put forward.² Box 1 lists the diagnostic criteria.

Patients are often described—wrongly—as being confused. TGA presents classically with an abrupt onset of severe anterograde amnesia. It is usually accompanied by repetitive questioning. The patient does not have any focal neurological symptoms. Patients remain alert, attentive, and cognition is not impaired. However, they are disoriented to time and place. Attacks usually last for 1–8 h.

Attacks are often precipitated by a Valsalva manoeuvre or physical activity including swimming, immersion in cold water, intercourse, acute pain, cerebral angiography, coughing, straining to defecate, heavy lifting, sawing and pumping.³ Psychological stressors (eg, arguments) are also well-recognised precipitants.

DIFFERENTIAL DIAGNOSIS

The key differential diagnoses which need to be considered are

- acute confusional state (ACS)
- complex partial seizures (CPS)
- transient epileptic amnesia (TEA)
- psychogenic amnesia
- transient ischaemic attack (TIA).

In ACS, patients are unable to maintain a coherent stream of thought, but patients with TGA can maintain a coherent stream of thought. Inattention is the key deficit in ACS, whereas TGA patients remain attentive. Hence, the ability to perform serial sevens or spell WORLD backwards is impaired in ACS, whereas it is not affected in TGA. Although in both conditions disorientation to time exists, repetitive questioning often occurs in TGA, whereas it does not usually occur in ACS. This is due to lack of insight in the latter.

Differentiating CPS from TGA can be difficult when the patient presents in the postictal state. However, during the episode, patients with CPS

Abbreviations: ACS, acute confusional state; CPS, complex partial seizures; DWI, diffusion-weighted imaging; TEA, transient epileptic amnesia; TGA, transient global amnesia; TIA, transient ischaemic attack

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Box 1 Diagnostic criteria²

- Attack must be witnessed.
- Acute onset of anterograde amnesia must be present.
- No alteration in consciousness must be present.
- No cognitive impairment other than amnesia must be present.
- No loss of personal identity must be present.
- No focal neurology or epileptic features must be present.
- No recent history of head trauma or seizures must be present.
- Attack must resolve within 24 h.
- Other causes of amnesia must be excluded.

exhibit automatisms and often blankly stare unlike patients with TGA who are alert, attentive and question repetitively. Further, recurrence is rare in TGA. Adherence to the criterion that the witness should have observed the episode before making the diagnosis of TGA will markedly reduce mistaking CPS for TGA. The differentiation can be complicated further by the possible occurrence of exclusive amnesia as a manifestation of CPS.

TEA is a distinctive manifestation of temporal lobe epilepsy (CPS) causing amnesia alone. It usually occurs in middle or old age and closely resembles TGA. Repetitively asking the same question is typical for TGA, but can also be observed with TEA. However, attacks of TEA tend to be more numerous than TGA. Episodes of TEA are usually relatively brief and most of them last for less than an hour. The occurrence of attacks on waking is characteristic for TEA. Persistent impairment of retrograde memory is more common in TEA.

Psychogenic amnesia usually occurs in the younger population and there is usually a precipitating psychosocial stressor. It is associated with memory loss for personal identification, indifference to memory loss, and retrograde rather than anterograde amnesia. One common variety of this rare problem involves profound retrograde amnesia with loss of personal identity in the face of normal anterograde memory.

Table 1 Key features which help to differentiate TGA from other conditions

ACS Unable to maintain a coherent stream of thought Inattention is prominent Performing serial sevens impaired	TGA Can be maintained Attentive Performing serial sevens not affected
Repetitive questioning not usually present	Characteristic
CPS Exhibit automatisms Stare blankly Recurrence common	TGA Alert, attentive Question repetitively Recurrence rare
TEA Short duration of less than an hour Frequent recurrence Occurrence on waking is characteristic	TGA Typical attack 4–6 h Recurrence uncommon No such predilection
Psychogenic amnesia Personal identity lost Can learn new information at times	TGA Personal identity intact Can never learn new information
Not distressed by amnesia Age group affected: young	Distressed by amnesia Middle-aged and elderly

ACS, acute confusional state; CPS, Complex partial seizures; TEA, Transient epileptic amnesia; TGA, transient global amnesia.

TGA can be confused with TIAs, as temporary disturbances in memory can accompany the more usual temporary motor and sensory symptoms of a TIA. However, if these motor and sensory symptoms accompany any memory disturbance, then a diagnosis of TIA must be made, which will require different investigations and has different implications from TGA.

Korsakoff psychosis, infarction, and tumours of hippocampus and other memory-relevant structures can cause prolonged amnesia. Korsakoff psychosis typically occurs in chronic alcoholism and is characterised by profound anterograde amnesia and retrograde amnesia. Patients often confabulate and usually lack insight into their deficits.

Table 1 lists the key features helping the differentiation of TGA from other conditions.

Often, patients present after the cessation of the episode. In such cases, and if a source for collateral history is available, history should be directed at eliciting the presence or absence of the following:

- personal identity
- features of automatisms
- staring
- repetitive questioning
- dysphasia (comprehension, spontaneous speech)
- specific precipitating factor (Valsalva-related manoeuvres)
- any previous episodes

as well as

- duration of the episode
- type of memory lost—immediate, recent or remote

AETIOLOGY AND PATHOGENESIS

Although the aetiology remains controversial, there is consensus that areas involved are mediobasal temporal region, the hippocampus and the parahippocampus. However, there is no agreement on the aetiopathogenesis of TGA. TIA, epilepsy, migraine, paradoxical emboli, venous congestion with consecutive ischaemia of memory-relevant structures and spreading depression of cortical activity have all been mooted as potential causes.

Different modalities of neuroimaging have played a significant role in localising the site of pathology. Single photon emission computed tomography revealed a decrease in cerebral blood flow in the temporal lobe and hippocampal region in most patients with TGA.⁴ Many investigators have used diffusion-weighted imaging (DWI) in TGA and contradictory findings have been reported,^{4–7} possibly because the sensitivity of DWI changes over time. Sedlaczek *et al*⁸ showed with serial imaging that DWI changes were rarely noted in the acute phase after attack, but were visible at 48 h.

The quick onset and recovery of the condition, and its frequent Valsalva triggers, led to the suggestion that it may result from a paradoxical embolus through a patent foramen ovale.⁹ However, Maalikjy *et al*¹⁰ did not find any significant difference in the prevalence of patent foramen ovale in patients with TGA. Furthermore, a theory suggesting that TGA is caused by paradoxical emboli rather than arterial emboli would have difficulty explaining why an arterial embolism would not cause the same clinical sequelae as a venous thrombus taking the same final route.

Epilepsy is thought to be unlikely as a cause of TGA, as the attacks occur in clear consciousness and have a low recurrence rate. Furthermore, the EEG recording is characteristically normal after the attack and even when EEG was performed during the attack it was unremarkable.¹¹ It is likely that the few TGA patients who later present with epilepsy were initially misdiagnosed as TGA. One study followed a cohort of presumed patients with TGA

and found that 9% of patients later presented with epilepsy.² However, all of their subsequent seizures culminated with postictal amnesia, and 50% of them had presented initially with an amnesic episode lasting for less than an hour.

The migraine theory proposes that glutamate release (which could be caused by emotional events as seen at the onset of TGA) in the hippocampus causes a spreading depression with transient dysfunction of the hippocampus.³⁻¹² Although some have reported an association of migraine with TGA,¹³ others have not found an increased incidence of migraine in TGA sufferers.¹⁰ Furthermore, migraine is a condition which generally occurs in the age range 25–55 years,¹⁴ quite distinct from the TGA, which is vanishingly rare under the age of 40 years.

Pantoni *et al*¹⁵ suggested that psychological disturbances may play a role in TGA. They observed that the trigger factors often involve emotional arousal and anxiety, and claimed that 50% of the patients with TGA demonstrate a phobic personality trait. They compared patients with TGA with those with TIA, and found a significantly higher rate of psychiatric disease and family history of psychiatric disease in patients with TGA. They proposed that hyperventilation leading to cerebral vasoconstriction might play a role in the aetiology.

The sudden onset of TGA might imply an ischaemic origin, be it venous or arterial. However, many case-control studies comparing patients with TGA with age-matched controls or with patients with TIA show that patients with TGA have fewer cardiovascular risk factors and a better prognosis than those with TIA, making thromboembolic arterial ischaemia an unlikely mechanism.

Lewis³, however, suggested that TGA may result from venous ischaemia. TGA often begins with a Valsalva maneuver, which allows brief retrograde transmission of high venous pressure to the cerebral venous system. The hippocampus (at least in pigs) is the area of the brain most sensitive to damage by such pressure,¹⁶ which would help explain why TGA occurs in the absence of other neurological symptoms. Such an increase in venous pressure would be more significant in the presence of incompetent internal jugular valves. Maalikjy *et al*¹⁰ showed that 90% of those patients who reported Valsalva maneuvers at the onset of their TGA had incompetent internal jugular valves, compared with 41% (a similar rate to the control group) of those patients with TGA who did not report such activities. It is tempting to conclude that patients with TGA can be divided into one group with incompetent valves whose episode was triggered by a Valsalva, and another group with a different aetiology. However, Lewis's theory³ does not explain why the incidence of TGA is so low given the high prevalence of incompetent jugular valves and Valsalva maneuvers.

Recently, a unifying hypothesis has been put forward by Winbeck *et al*⁷ in that TGA can result from transient ischaemia of memory-relevant structures either from an arterial emboli or from venous ischaemia with Valsalva-like activities before the onset of symptom.⁷ They suggested that DWI may not be sensitive to pick up abnormalities in all patients with TGA, particularly when it is due to venous congestion.

Hence, it is possible that TGA may result from different mechanisms such as venous congestion with Valsalva-like activities before symptom onset, arterial thromboembolic ischaemia and vasoconstriction due to hyperventilation.

INVESTIGATIONS

Sandson and Price¹⁷ suggest MRI, magnetic resonance angiography, EEG, ECG, ECHO (with bubble study), holter and toxicology screen in investigations. Brown disputes the need for these investigations if the diagnosis is clear.¹⁸ We agree that the diagnosis may be made safely in the presence of a characteristic collateral history, and in such a situation no investigations are necessary. However, if the diagnosis is not entirely clear, we believe it is reasonable to perform an MRI and EEG.

PROGNOSIS

Recurrence is rare and the reported risk of a recurrent attack within 5 years varies between 3% and 20%.

DRIVING

The Driver and Vehicle Licensing Agency (DVLA) of the United Kingdom stipulates no restriction on driving for both groups 1 and 2. For Group 1, it states that provided epilepsy, any sequelae from head injury and other causes of altered awareness have been excluded, there is no restriction on driving. For group 2, a single confirmed episode is not a bar to driving, and the licence may be retained. If two or more episodes occur, driving should cease and DVLA be notified. Specialist assessment is advised to exclude all other causes of altered awareness.

TREATMENT

No specific treatment is indicated for a typical episode. If there is any possibility of TIA, epilepsy or migraine, that should be treated accordingly.

SUMMARY

TGA presents in a dramatic manner with abrupt onset of memory loss of recent events and inability to retain new information, which resolves spontaneously. Currently there is no agreement on the aetiology of TGA, although several theories have been suggested. Most of the patients do not have significant vascular risk factors. Recurrence is rare.

MULTIPLE CHOICE QUESTIONS: (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

1. Transient global amnesia (TGA)
 - a) is characterised by retrograde amnesia and may be associated with anterograde amnesia
 - b) is most common below 40 years of age
 - c) occurs almost exclusively in men
 - d) is characterised by intact higher cortical function
2. During the attack of TGA
 - a) there is clouding of consciousness
 - b) there is no focal neurology
 - c) there is always anterograde amnesia
 - d) personal identity of the patient is intact
3. TGA
 - a) is commonly precipitated by activities involving Valsalva maneuver
 - b) is never precipitated by emotional stress
 - c) is strongly associated with patent foramen ovale
 - d) is rarely associated with vascular risk factors
4. With regard to TGA
 - a) recurrence is very common
 - b) driving is banned
 - c) DWI is always negative
 - d) attacks always last for <24 h

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REFERENCES

- 1 **Zeman AZ**, Hodges JR. Transient global amnesia. *Br J Hosp Med* 1997;**58**:257–60.
- 2 **Hodges JR**, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. *J Neurol Neurosurg Psychiatry* 1990;**53**:834–43.
- 3 **Lewis SL**. Aetiology of transient global amnesia. *Lancet* 1998;**352**:397–9.
- 4 **Sander K**, Sander D. New insights into transient global amnesia: recent imaging and clinical findings. *Lancet Neurol* 2005;**4**:437–44.
- 5 **Gass A**, Gaa J, Hirsch J, *et al*. Lack of evidence of acute ischemic tissue change in transient global amnesia on single-shot echo-planar diffusion-weighted MRI. *Stroke* 1999;**30**:2070–2.
- 6 **Huber R**, Aschoff AJ, Ludolph AC, *et al*. Transient global amnesia. Evidence against vascular ischemic etiology from diffusion weighted imaging. *J Neurol* 2002;**249**:1520–4.
- 7 **Winbeck K**, Etgen T, von Einsiedel HG, *et al*. DWI in transient global amnesia and TIA: proposal for an ischaemic origin of TGA. *J Neurol Neurosurg Psychiatry* 2005;**76**:438–41.
- 8 **Sedlacek O**, Hirsch JG, Grips E, *et al*. Detection of delayed focal MR changes in the lateral hippocampus in transient global amnesia. *Neurology* 2004;**62**:2165–70.
- 9 **Klotzsch C**, Sliwka U, Berlitz P, *et al*. An increased frequency of patent foramen ovale in patients with transient global amnesia. Analysis of 53 consecutive patients. *Arch Neurol* 1996;**53**:504–8.
- 10 **Maalikiy N**, Agosti C, Anzola G, *et al*. Transient global amnesia: a clinical and sonographic study. *Eur Neurol* 2003;**49**:67–71.
- 11 **Cole AJ**, Gloor P, Kaplan R. Transient global amnesia: the electroencephalogram at onset. *Ann Neurol* 1987;**22**:771–2.
- 12 **Strupp M**, Bruning R, Wu R, *et al*. Diffusion-weighted MRI in transient global amnesia: elevated signal intensity in the left mesial temporal lobe in 7 of 10 patients. *Ann Neurol* 1998;**43**:164–70.
- 13 **Frederiks JA**. Transient global amnesia. *Clin Neurol Neurosurg* 1993;**95**:265–83.
- 14 **Lipton RB**, Stewart WF. The epidemiology of migraine. *Eur Neurol* 1994;**34**(Suppl 2):6–11.
- 15 **Pantoni L**, Bertini E, Lamassa M, *et al*. Clinical features, risk factors, and prognosis in transient global amnesia: a follow-up study. *Eur J Neurol* 2005;**12**:350–6.
- 16 **Ye J**, Yang L, Del Bigio MR, *et al*. Neuronal damage after hypothermic circulatory arrest and retrograde cerebral perfusion in the pig. *Ann Thorac Surg* 1996;**61**:1316–22.
- 17 **Sandson TA**, Price BH. Transient global amnesia. *Semin Neurol* 1995;**15**:183–7.
- 18 **Brown J**. ED evaluation of transient global amnesia. *Ann Emerg Med* 1997;**30**:522–6.

ANSWERS

- 1) a)F, b)F, c)F, d)T.
- 2) a)F, b)T, c)T, d)T.
- 3) a)T, b)F, c)F, d)T.
- 4) a)F, b)F, c)F, d)T.

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